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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,095	11/18/2003	Alexandra Kaczmarek	21489	5755

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HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER

PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
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1648

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/716,095	Applicant(s) KACZMAREK ET AL.	
	Examiner Jeffrey S. Parkin	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☒ Claim(s) 1-5 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection on 02 April, 2009. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Claims 1-5 are pending in the instant application.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Oldenburg et al. (1994) in view of Lambert et al. (2000), Mukhopadhyay (1997), McCoy et al. (1991), and Vendenbark (1997). The claims have been amended to specify that the inclusion bodies containing the proteins of interest are

solubilized at a pH of at least 9.0 in the absence of detergents or denaturing agents.

As previously set forth, Oldenburg and colleagues disclose a recombinant parathyroid hormone analog, rPTH(1-34*), was obtained from *Escherichia coli* using a gene polymerization strategy. The PTH gene polymer contains up to 8 copies of the gene, each separated by a cleavable linker. The polymer was expressed at very high levels and formed inclusion bodies which could be easily isolated by low-speed centrifugation. A polyhistidine leader peptide allows rapid purification via nickel chelation chromatography of the PTH polymer solubilized from the inclusion bodies. Yields of greater than 500 mg/liter have been obtained. After isolating the polymer, monomeric rPTH(1-34*) is released from the polymer by chemical cleavage with cyanogen bromide. Following cyanogen bromide cleavage and high-performance liquid chromatography purification, highly purified, biologically active rPTH(1-34*) is obtained at a yield of approximately 300 mg/liter. This teaching provides a general strategy for the high-level production of a variety of peptides and small proteins using inclusion bodies. This teaching does not provide antifusogenic polypeptides.

Lambert and colleagues provide a number of antifusogenic peptides comprising DP178 (aa 638-673). These peptides are potent inhibitors of HIV-1 replication.

Mukhopadhyay (1997) provides a detailed review concerning the purification of proteins from inclusion bodies. Various formats are disclosed including the utilization of a denaturing agent at

the recited range. Moreover, this teaching provides detailed formats for solubilizing inclusion bodies including the utilization of high pH buffers. The author also provided routine criteria to employ when assessing which solvent to employ (see last paragraph, p. 85).

McCoy and associates (1991) provide detailed methodologies for solubilizing inclusion bodies containing a biologically active polypeptide through the utilization of high pH buffers (see the claims and representative examples). The authors noted that high pH buffers were an economical means for solubilizing inclusion bodies. It was also noted that denaturing agents and detergents suffered from a number of limitations when attempting to produce large quantities of the soluble, active protein.

Finally, Vandenbark (1997) teaches the inclusion of C-terminal glycine residues in polypeptides is useful because it facilitates their conjugation to other carrier molecules or it facilitates their synthesis during solid-phase syntheses.

Therefore, it would have been *prima facie* obvious at the time of the invention to utilize the polypeptide inhibitors of Lambert *et al.* (2000), in the protocols of Oldenburg *et al.* (1994), since this would facilitate the high-level production of purified peptide. One of ordinary skill in the art would also be motivated to employ the purification protocols provided by Mukhopadhyay (1997) and McCoy *et al.* (1991), since this would also facilitate the high-level production of peptide. One of ordinary skill in the art would have been further motivated to incorporate a C-terminal Gly, as taught by Vandenbark (1997), to

facilitate the synthesis of the fusion peptides or the conjugation to a carrier molecule.

Response to Arguments

Applicants traverse and submit that Oldenburg differs in at least four of the claimed elements which are not remedied by the additional references relied upon. Oldenburg and colleagues unequivocally demonstrate that tandem repeats of a biologically active polypeptide can be isolated and purified utilizing inclusion bodies. As previously set forth, this reference provides a general strategy for the high-level production of a variety of peptides and small proteins using inclusion bodies. The claimed elements allegedly lacking are clearly provided by the additional references relied upon.

It was additionally argued that Lambert *et al.* (2000) also fails to remedy any of the deficiencies in Oldenburg. Contrary to applicants' assertion, this teaching clearly provided a number of antifusogenic peptides comprising DP178 (aa 638-673) which are potent inhibitors of HIV-1 replication. Thus, this teaching clearly supplies an antifusogenic peptide as required by the claim language.

Additional arguments were provided suggesting that Mukhopadhyay (1997) also failed to address any of the deficiencies in Oldenburg. This argument is also incorrect. As previously set forth, this teaching provides a detailed analysis of routine inclusion body purification protocols, including the utilization of high pH buffers. The author also provided routine criteria to employ when assessing which solvent to employ (see

last paragraph, p. 85). Thus, one of ordinary skill in the art need only select from a limited number of possibilities (e.g., GuHCL, SDS, or high pH) to ascertain the most suitable purification protocol.

Finally, it was also argued that Vandembark (1997) fails to remedy any of the deficiencies of Oldenburg. Once again applicants' arguments are not tenable. Vandembark clearly teaches the inclusion of C-terminal glycine residues in polypeptides is useful because it facilitates their conjugation to other carrier molecules or it facilitates their synthesis during solid-phase syntheses. Thus, one of ordinary skill in the art would have been motivated to modify the antifusogenic HIV-1 polypeptides of Lambert et al. (2000) to include a C-terminal glycine. This would obviously facilitate the conjugation of these molecules to other carrier proteins after purification.

Applicants are reminded that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 U.S.P.Q.2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851

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F.2d 1401, 1403, 7 U.S.P.Q.2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). Methods for the purification of biologically active proteins using inclusion bodies were well-known in the prior art. Various solubilization methods were also well-known in the prior art. In fact, applicants' own disclosure also states that purification methods employing inclusion bodies were well-known (see p. 15). The crux of the invention appears to be directed toward the "surprising" discovery that the claimed fusion proteins were capable of being purified using a high pH buffer. There is nothing surprising about this finding, particularly in view of the teachings of McCoy et al. (1991), who clearly demonstrate that biologically active proteins can be purified from inclusion bodies by solubilization at high pH. Therefore, the claimed invention is clearly *prima facie* obvious in view of the teachings of the prior art.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Larry R. Helms, can be reached at (571) 272-0832. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

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Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

21 June, 2009